Effects of ketamine infusion on breathing and encephalography in spontaneously breathing ICU patients

Aiman Suleiman, MD, MSc[1,2,3], Peter Santer MD, DPhil[1], Ronny Munoz-Acuna, MD[1], Maximilian Hammer, cand.med.[1], Maximilian S. Schaefer, MD, PhD[1,2,4], Luca J. Wachtendorf, cand.med.[1,2,5], Sandra Rumyantsev, PharmD[6], Lorenzo Berra, MD[7], Shubham Chamadia, PhD[7], Oluwaseun Johnson-Akeju, MD, MMSc[7,8], Elias N. Baedorf-Kassis, MD[9], Matthias Eikermann, MD, PhD[5,10]

[1] Department of Anesthesia, Critical Care & Pain Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA

[2] Center for Anesthesia Research Excellence (CARE), Beth Israel Deaconess Medical Center, Boston, MA 02215, USA

[3] Department of Anesthesia and Intensive Care, Faculty of Medicine, University of Jordan, Amman, Jordan

[4] Department of Anesthesiology, Duesseldorf University Hospital, Germany

[5] Department of Anesthesiology, Montefiore Medical Center and Albert Einstein College of Medicine, Bronx, NY 10467, USA

[6] Pharmacy, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA

[7] Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA

[8] McCance Center for Brain Health, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA

[9] Department of Medicine, Division of Pulmonary and Critical Care, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA

[10] Klinik für Anästhesiologie und Intensivmedizin, Universität Duisburg-Essen, Essen, Germany

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Corresponding author: Matthias Eikermann, MD, PhD

Department of Anesthesiology, Montefiore Medical Center, Albert Einstein College of Medicine, 111 East 210th Street, Bronx, NY 10467, USA

Email: meikermann@montefiore.org

Phone: (718) 920-2802

Fax: (718) 920-4327

Study protocol

I. Background

Sedation is frequently required in the intensive care unit (ICU) to control agitation associated with mechanical ventilation. However, heavy sedation is associated with prolonged ICU and hospital stays.[1] Pain is a common experience for most ICU patients,[2] and failure to recognize that pain may result in excessive administration of sedatives.[3] Accordingly, an aggressive approach to manage pain has been strongly recommended by published consensus in the ICU.[3]

Management of pain in critically ill surgical patients can be very challenging. Large doses of opioids are frequently required to alleviate pain for ICU patients; however, opioids administration is associated with a number of adverse effects, such as nausea, vomiting, depressed gastrointestinal motility, drowsiness and at larger doses, respiratory depression. Furthermore, opioids when used alone in large doses for a prolonged period can induce tolerance, which may lead to increased postoperative pain.[4] Non-opioid analgesics, such as nonsteroidal anti-inflammatory drugs and acetaminophen are frequently used as adjuncts to opioids for pain. However, the efficacy of those adjuncts may be limited, and significant side effects, gastritis, ulcers, bleeding, and perforation also limit the use of these drugs in certain critically ill patient populations, such as postsurgical or trauma patients.[5]

Maintaining the patency of upper airway in sedated and anesthetized patients is challenging especially when patients are ready to be weaned from mechanical ventilation. Spontaneous breathing trial (SBT) is a common technique utilized to expedite the weaning process.[6] This technique often requires the reduction and/or discontinuation of sedatives and analgesics. In some surgical patients, reducing these medications can lead to pain associated agitation and inability to conduct SBTs. In response to their pain by adding or resuming sedatives or analgesics that cause respiratory depression may lead to a prolonged need for mechanical ventilation. Initiating medications that provide narcotic sparing effects without causing respiratory depression may allow for the reduction or discontinuation of agents that depress respiratory drive and subsequently facilitate extubation.

In addition, impairment of airway patency is a common cause of extubation failure, and opioids and hypnotics can adversely affect airway patency. Opioids are respiratory depressants and induce a dose-dependent impairment of upper airway dilator muscle activity. Hypnotics and sedatives, including propofol, dexmedetomidine and midazolam predispose the upper airway to collapse, at least in part by decreasing upper airway muscle activity. As the transition is made from the awake to anesthetized states, all hypnotics and sedatives so far studied consistently impair upper airway integrity.

Ketamine, a noncompetitive antagonist of N-methyl-D-aspartate (NMDA), is used as an anesthetic and analgesic and has been shown to reduce opioid consumption after abdominal and orthopedic surgery.[7,8] By blocking NMDA receptors, ketamine can prevent the development of opioid tolerance.[9] In addition, ketamine unlike other anesthetics activates respiratory effort[10] and promotes bronchodilation.[11] At subanesthetic plasma concentrations, ketamine reduces both opioid and propofol requirements. It is further known, that dexmedetomidine in combination with ketamine provides better hemodynamic stability and sedation than dexmedetomidine alone.[12] Interestingly dexmedetomidine and propofol induced sedation, reduce the ventilator response to a similar extent.[13] Recent animal data also suggest that when added to propofol in a sedation regimen, ketamine decreased hypoventilation when compared to propofol alone because ketamine can increase genioglossus phasic activity while abolishing the coupling between loss of consciousness and upper airway dilator muscle activity.[14] However, this relationship has not been examined in humans in combination with other sedatives and analgesics. In addition, the respiratory stimulating effects of ketamine may also be harmful since they may increase the transpulmonary pressure which in turn may increase the vulnerability to respiratory failure under specific conditions.[15]

Ketamine has been used for many years in critically ill patients for sedation and analgesia, including the MGH and BIDMC ICUs. The purpose of this pharmaco-physiological interaction trial is to evaluate the effects of ketamine at a subanesthetic dose on breathing and electroencephalography. The target population will include mechanically ventilated patients deemed suitable for spontaneous breathing trial based on standard MGH/BIDMC criteria and deemed a candidate to receive low-dose ketamine by the primary critical care team. Spirometry will be utilized to evaluate upper airway patency. The Sedline brain function monitor will be used to evaluate the effects of ketamine on EEG during wakefulness and sleep. A standard nutritional nasogastric tube or esophageal balloon catheter will be inserted to measure esophageal pressure, which enables us to measure the effects of ketamine on transpulmonary pressure. A volumetric

capnography, NICO noninvasive device from Respironics (Hartford, CT), will be used to measure anatomical dead space, CO_2 production, mean expiratory CO_2 and slope of the alveolar plateau of the volumetric capnogram.

II. Hypothesis

The objective of this study is to evaluate the effects of ketamine on breathing and electroencephalography in mechanically ventilated patients. The study is designed as a prospective, open label, pharmaco-physiologic interaction study with anticipated enrollment of 15 patients. We will test the hypothesis that ketamine drip at a subanesthetic infusion rate (low dose ketamine 5 – 10 mcg/kg/min) has respiratory stimulating effects.

Primary outcome

- Respiratory function: inspiratory flow measured 15 minutes prior to initiation of ketamine infusion (to serve as baseline), at 60 minutes of ketamine infusion at 5mcg/kg/min, at another 60 minutes of infusion at 10mcg/kg/min, at which point the infusion is stopped for 3 hours for a final set of measurements.

Secondary endpoints

- EEG measurements (Sedline brain function monitor).
- Tidal volume, respiratory rate, respiratory timing (duty cycle), and minute ventilation.
- Work of breathing.
- End tidal CO2 (carbon dioxide).
- Transpulmonary pressure.

III. Subject selection

Subjects will be deemed eligible based on the following inclusion/exclusion criteria:

Inclusion Criteria:

- Adults ≥ 18 years admitted to MGH (Blake 12 ICU, Ellison 4 SICU) and BIDMC (SICU, T-SICU) requiring mechanical ventilation.

- The patient is deemed suitable for spontaneous breathing trial based on standard MGH/BIDMC criteria (*Please note*: These protocols reflect clinical practice and were used to establish eligibility. Aspects related to timing of SBTs and use of pressure support were modified for the study as described under *Study Procedures*):

    - **MGH PROTOCOL:**

        - **Step 1: Safety Screen – No Trial if**

            1. *ICP* Brain death, ICP > 15, suspected high ICP, or difficult to control ICP
            2. *NMB* Neuromuscular blockade
            3. *HPTS* Significant hemoptysis (significant amounts of blood from ETT or tracheostomy)
            4. *HEM* Hemodynamic instability
            5. *ARWY* Unstable Airway
            6. *FIO2* $F_IO_2 >$ 0.6
            7. *PC* Pressure control > 20 cm H2O
            8. *PEEP* $\geq$ 10 cm H_2O
            9. V_E $\geq$ 15 L/min
            10. *MD* SICU team consensus says no
            11. *ECLS* Extracorporeal life support

        - **Step 2: 2 minute screen – RN and RRT remain with patient**

1. PSV = 0, PEEP = 0, F_IO_2 unchanged

- **Step 3: SBT 30 minute trial**
    1. PSV = 0, PEEP = 0, F_IO_2 unchanged (if other settings are used, please record on SBT sheet)

- **Pass Without Extubation Codes**
    1. *WET* Fluid Overload
    2. *SECR* Secretions
    3. *WEAK* Pt too weak
    4. *MS* Mental Status
    5. *SED* Over sedated
    6. *ARWY* Unstable, unsafe, swollen airway
    7. *PDCR* Imminent/awaiting procedure
    8. *FMLY* Family Issues/DNI order
    9. *WORS* MD thinks patient will get worse
    10. *OTHR* No reason above applies

- **Stop trial at any point for:**
    1. APNC 30 seconds of apnea
    2. SOB Use of accessory muscles, nasal flaring present, subjective dyspnea
    3. AGIT Significant change in agitation or anxiety unresolved with reassurance
    4. ↑RR Tachypnea (rate > 30 bpm for > 5 min)
    5. ↓RR Slow breathing (rate $\leq$ 6/min)
    6. S_pO_2 Decreased S_PO_2 unresponsive to increased F_IO_2
    7. ISCH Ischemic ECG changes

- **Step 4: SICU team discusses plan to extubate within the next hour**

- **BIDMC PROTOCOL:**

  - **Screening and Plan**

    1. A weaning and sedation sheet will be completed by the day shift Respiratory Therapist for each unit which will include all intubated and mechanically ventilated patients.

    2. Eligibility for weaning will be discussed by the MD, RT, and RN between 5:00pm-10:00pm.

    3. Disqualifiers for spontaneous awakening trial (SAT) include:

       a. HR > 140 or < 55

       b. BP > 180 or < 90

       c. Active Ischemia/Arrhythmia

       d. Elevated ICP

       e. Use of Neuromuscular blocking agent

       f. Agitation (RASS 2-4)

       g. Unstable Airway

       h. Unstable Spine

       i. OR/Procedure

       j. Vent dependent/Trached

       k. CMO

    4. Disqualifiers for spontaneous breathing trial (SBT) include:

a. PEEP ≥10cmH_2O

b. SaO2 ≤ 90%

c. FiO2 ≥ 0.60

d. pH ≤ 7.35

Note: SAT disqualifiers can also disqualify for SBT.

- **Performing SBT**

1. SBT should be attempted on Night Shift for all eligible patients between 4:00am and 6:30am. SBT may be reassessed from 7:00am to 12:00pm if necessary.

2. To perform SBT, place patient on CPAP mode with a PEEP of 0cm and a PSV of 5cmH_2O for 30 minutes. FiO2 unchanged.

3. A RSBI (Rapid Shallow Breathing Index) should be obtained just prior to end of SBT (30 minutes) by:

   a. Measuring RR and MV for 1 minute on SBT.

   b. At end of 1 minute, divide the MV by the RR to calculate average VT.

   c. Then divide RR by VT to obtain RSBI.

   d. **NOTE:** Patients who are intubated with a 7.0 mm and smaller ET tubes may require some inspiratory assistance during the RSBI test. With ET tubes smaller than 7.5 mm, Automatic Tube Compensation (ATC) should be used instead of PSV during the RSBI test and the SBT.

4. SBT termination criteria include:

    a. RR > 35 b/min. for > 5 min.

    b. SpO_2 < 90% for > 2 min.

    c. Development of ectopy

    d. RSBI ≥ 105 for 5 minutes

    e. Heart rate > 140 b/min. or 20% increase or decrease from baseline

    f. Systolic BP > 180 mmHg or < 90 mmHg or 20% increase or decrease from baseline

    g. Excessive use of accessory muscles or paradoxical breathing.

    h. Increased anxiety/Diaphoresis

Once patient has successfully passed, patient will be placed on PEEP of 5cm H_2O and PSV 5cm H_2O. If a patient fails a SBT, they will be returned to previous ventilator settings and re-screened in ≤ 24 hours.

- **Daily Rounds**

1. Ventilator rounds will occur in each unit daily based on individually agreed times.

- **Extubation**

1. During rounds, MD will decide as to whether patient may or may not be extubated with the information provided.

2. Extubation Criteria includes:

    a. Successful completion of SBT

b. Effective secretion clearance

c. Adequate airway protection

d. Confirmed with MD/Order in POE.

- The patient is deemed a candidate to receive low dose ketamine by the primary critical care team.
- The patient has been maintained at a constant infusion rate of propofol or dexmedetomidine and hydromorphone or morphine for at least 3 hours prior to initiating low dose ketamine.
- Patients with established IV access (for other medical reasons), which can be used to infuse intravenous ketamine.

Exclusion Criteria:

- Age < 18 years
- Esophageal injury (bleeding varices, hematamesis, esophageal trauma, need for esophageal surgery)
- Allergic to ketamine
- Active alcohol/drug abuse and history of opiate dependence
- Known neurodegenerative disorders
- Major neurologic disorders (elevated ICP)
- Subjects who pass a trial of SBT and can be extubated or with a plan for extubation
- Subjects with a platelet count of less than 20,000

IV. Subject Enrollment

Subjects will be identified from MGH (Blake 12 SICU, Ellison 4 SICU) and BIDMC (SICU, T-SICU) census on a daily basis between the hours of 7:30 am and 10:00 pm by study personnel and identified by other SICU clinicians. The consent discussion will begin at least 24 h before the initiation of study-related procedures to allow potential patients/their legally authorized representative to reflect on the potential benefits and risks and possible discomforts of participation. We will utilize the progress report and medical history when the patient is first admitted to the ICU to determine if the patient has a history of substance use disorder. We will also reconfirm with the primary team if a patient that meets the inclusion criteria has no history with substance use disorder.

If identified subjects meet inclusion/exclusion criteria, they will then be approached by a specialized health care provider. The specialist health care provider will be a physician that is part of the clinical staff in the ICU who has firsthand knowledge of the subject's medical history. This physician will approach potentially eligible subjects to introduce them to the research study. If both the specialist health care provider approved his or her subject to be contacted for research purposes and the subject agrees to be contacted by study staff discussed verbally during the course of providing medical care, a study physician will then approach the subject to obtain informed consent.

The study physician will meet with the legally authorized representative of the potential subject to review and to discuss the details of the research study using the informed consent document as a guide. This discussion will include all of the required elements of informed consent, e.g. the purpose of the research, the procedures to be followed, the risks and discomforts as well as potential benefits associated with participation.

The legally authorized representative of potential subjects are then given a copy of the informed consent document so they can carefully read the document and discuss the research with their family, friends and/or physician and develop questions to ask at their next meeting with the research staff. Once they have read the consent document and their questions are answered, if they agree to participate in the research, they sign and date the informed consent document.

The following categories of surrogates may provide consent in writing on behalf of potential subjects' incapable of providing informed consent:

1. Court appointed guardian with specific authority to consent to participation in research or authority to make health care decisions for a class of diagnostic and therapeutic decisions inclusive of the proposed research;
2. Health care proxy/person with durable power of attorney with specific authority for making health care decisions inclusive of the proposed research; or
3. Spouse, adult child, or other close family member who knows the subject well and has been involved in their care.

Assent of subjects will be a requirement for participation in the research unless the subject is incapable of giving assent due to his/her medical condition. If the individual objects to participation, s/he should not be enrolled. When surrogate consent is relied upon, the investigator must ensure that the surrogate understands that his or her decisions should be based on "substituted judgment." This means that the decision reflects a potential subject's own views when s/he had the capacity to express them. Investigators will document the relationship of the surrogate to the subject in the research record.

If a patient is sedated or delirious, and no family members or healthcare proxy will be present in the next 24 hours of ICU admission, obtaining written consent via email or fax of a family member will be considered as an acceptable form of consent. After the responding clinician confirms the eligibility of the patient, he or she will first contact the surrogate to introduce them to the physician investigator. The investigator will then explain the research protocol in detail over the phone, including the study procedure, risks and benefits of the study, and the privacy rights of the patient. If the surrogate would like to provide consent, a pdf copy of the full consent form will be emailed for review. The investigator will ask the surrogate to email or fax the consent form back. All study consent forms will be sent in accordance MGH/Partners Information Security guidelines.

V. Study procedures

Low-dose ketamine protocol

Consented subjects who meet inclusion and exclusion criteria will start ketamine infusion at 5mcg/kg/min for one hour after which the infusion rate will be increased to 10mcg/kg/min for another hour. At the end of the 2 hours, ketamine infusion will be discontinued. The ketamine dose used in the study is within the recommended range per MGH intravenous drug policy for intubated patients. A trial of spontaneous breathing (SBT) with PEEP=0 and no pressure support for 1 minute will be performed at 3 specific times - prior to initiation of ketamine, 1 hour post infusion of at 5mcg/kg/min and 1 hour post infusion at 10 mcg/kg/min. During these times, respiratory function measurements will be made (see below). Subjects who pass the SBT and can be extubated prior to enrollment or subjects who pass the SBT with a plan to extubate will not be included.

Measurement of respiratory function

Respiratory flow will be measured using a pneumotach (Hans Rudolph Inc., Shawnee, KS) connected to the ventilation tubing of the patient during the spontaneous breathing trials. Inspiratory flow, tidal volume, and minute ventilation, as well as respiratory rate and duty cycle (inspiratory time/total time of respiratory cycle) will be measured.

Measurement of arousal state and respiratory effort

Electroencephalography (EEG)-based arousal state and respiratory effort will be continuously measured in all subjects using the the Sedline brain function monitor (Masimo Corporation, Irvine, CA), as shown in a previous study.[16] The measurement will start prior to initiation of ketamine and continued until 3 hours after the end of ketamine infusion.

Measurement of esophageal pressure

A standard nutritional nasogastric tube with an integrated esophageal balloon or an esophageal balloon catheter will be inserted if not already in place by a trained physician or respiratory therapist prior to initiation of ketamine and will be used for measurement of transpulmonary pressure for the study period

(approximately 5 hours). The correct positioning will be checked by changes of waveforms when withdrawn from the stomach into the esophagus and by the occlusion test.

Measurement of CO_2 monitoring

Opioids are known to affect respiratory control and ventilatory response to blood CO_2 levels. Ketamine has potential effects on pulmonary ventilation distribution. For these reasons, volumetric capnography, a noninvasive technique that allows for the computation of expired volume versus carbon dioxide partial pressure curve, will be performed during the study and utilized to estimate variables quantifying pulmonary CO_2 exchange and ventilatory distribution. These variables will include anatomical dead space, CO_2 production, mean expiratory CO_2 (for computation of physiological dead space), and slope of the alveolar plateau of the volumetric capnogram (phase III, a measure of ventilation heterogeneity). Measurements will be performed using the NICO© device from Respironics (Hartford, CT). Periods of at least five minutes during steady state breathing will be recorded before and after administration of ketamine and stored for posterior analysis.

Routine medical care

During the study period, there is no limitation on the medical care the patient would otherwise receive. Specifically, the patient may receive other analgesics and sedatives as deemed appropriate by the primary team at the time of the ketamine infusion and the subsequent washout period.

VI. Statistical methods, data analysis and interpretation

The main study endpoint is respiratory flow. We hypothesized that ketamine would increase inspiratory flow by 15% compared to baseline (null hypothesis: ketamine does not increase inspiratory flow). Assuming a baseline flow of 0.5±0.1 L/s, a 15% increase by ketamine, and 75% correlation between measurements, a one-tailed paired t-test with an alpha of 0.05 and a power of 80% resulted in a required sample size of 14 to detect a significant difference. To account for possible dropouts, we increased this number to 15.

VII. Risk and discomfort

Clinical evaluations of the patient will be made while on the study (five hours). We believe the risks to be small. During the respiratory and EEG measurement, subjects might find it uncomfortable or difficult to sleep while attached to the pneumotach or the Sedline brain function monitor. We will stay in close communication with the subjects and the clinical care team (nursing staff and physicians) to prevent this discomfort and remove all measurement devices on request or when clinically necessary. There may be other risks that are currently unknown.

Nasogastric Tube (NGT)

There is a potential risk of using the nasogastric tube, which includes nasopharyngeal or esophageal injury or perforation, aspiration, and discomfort. Inserting the nasogastric tube may be uncomfortable and could cause gagging or even vomiting, and a minimal risk of bleeding. The risk of discomfort will be minimized by maintaining subjects on propofol and hydromorphone or morphine. The subjects will have a tube in his/her esophagus and a secured airway with an endotracheal tube. The risk of aspiration will be minimized by having an experienced respiratory therapist or attending physician performs the procedure. The tube, once in place, does not induce the subject's gag reflex. The NGT has been demonstrated to provide successful, safe, and reliable NGT insertion without any side effect for obese patients by a prior study.

Risks associated with low dose ketamine use include hypertension, hypotension, tachycardia, bradycardia, and transient signs of emergence symptoms (confusion, adverse psychiatric symptoms). Adverse effects of ketamine are dose dependent and incidence of emergence symptoms are significantly less (<5%) with low dose ketamine. Subjects will also be on propofol which will further reduce the risks of emergence.

VIII. Potential benefit

Patients don't have a direct benefit by participating in the study. Information gathered from this study may help future patients receive optimal ketamine efficacy and safety monitoring.

IX. Monitoring and quality assurance

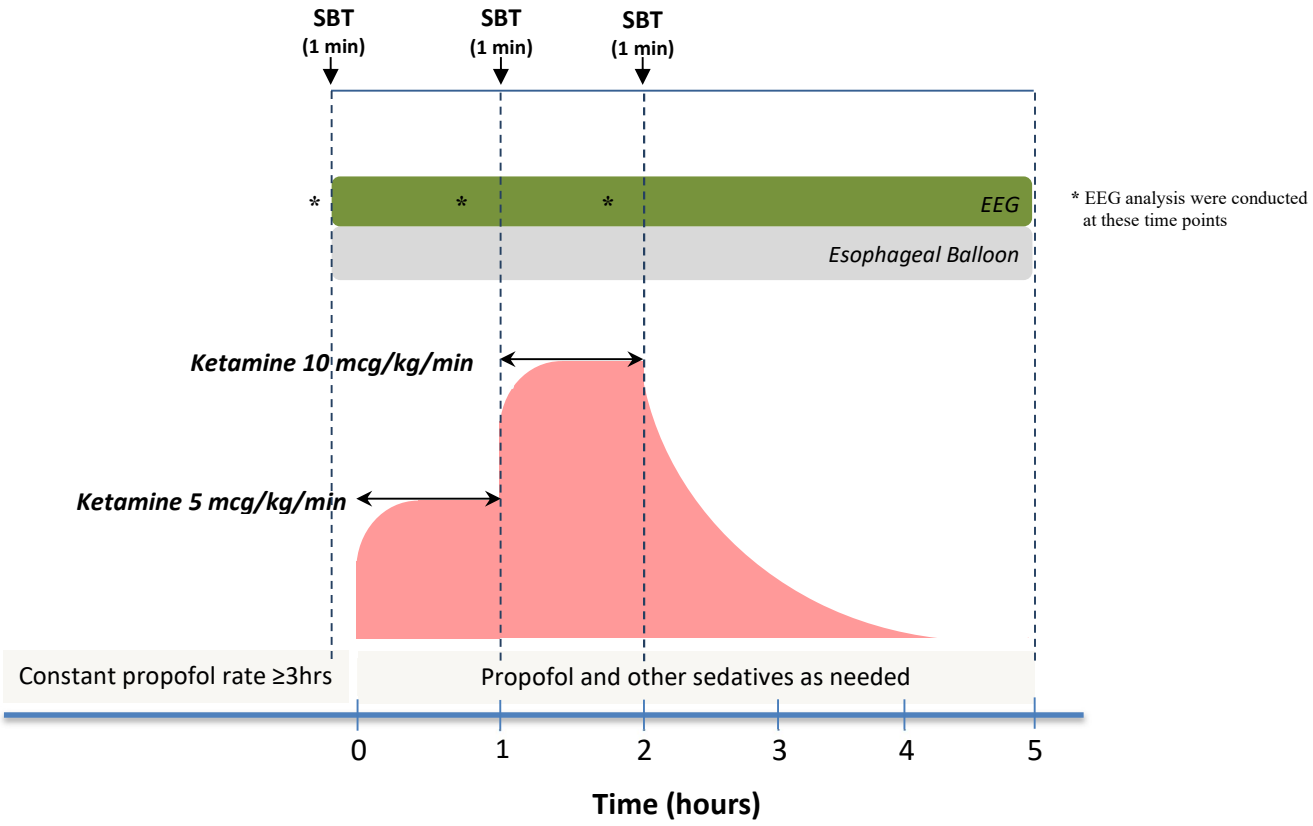
Patients will have sedation, pain and CAM-ICU assessed on a daily basis as part of routine ICU care. Patients will have respiratory rate assessed while they are on ketamine infusion as a standard of care in the ICU. Principle investigator will review the safety/efficacy data daily. Additionally, a physician investigator will review all hemodynamic monitoring pertinent to ketamine treatment. The principal investigator and study staff will meet after each time five subjects are enrolled to review data to ensure validity, adherence to IRB-approved protocol, patient ethics, security and confidentiality of protected health information, and submission of safety reports.

During ketamine infusion, if the patient develops hemodynamic instability (i.e., mean arterial pressure (MAP) change by ±25% from baseline, heart rate more than 150 bpm or less than 50 bpm, or parameters otherwise defined by the primary team) and this instability is perceived to be associated with ketamine use, the ketamine infusion will be stopped and the patient will be withdrawn from the study.

All adverse events (AEs) will be reported. AEs are defined as any unfavorable and unintended sign, symptom, or disease temporally associated with ketamine therapy. The relationship of any AE(s) to ketamine therapy will assessed by the clinician and reported as not related, unlikely, possibly, probably, or definitely related, and the intensity of the AE(s) as mild, moderate, or severe.

The PI will report adverse events or other unanticipated problems to the PHRC as described in the PHRC policy on Adverse Event Reporting and Unanticipated Problems Involving Risks to Subjects or Others.

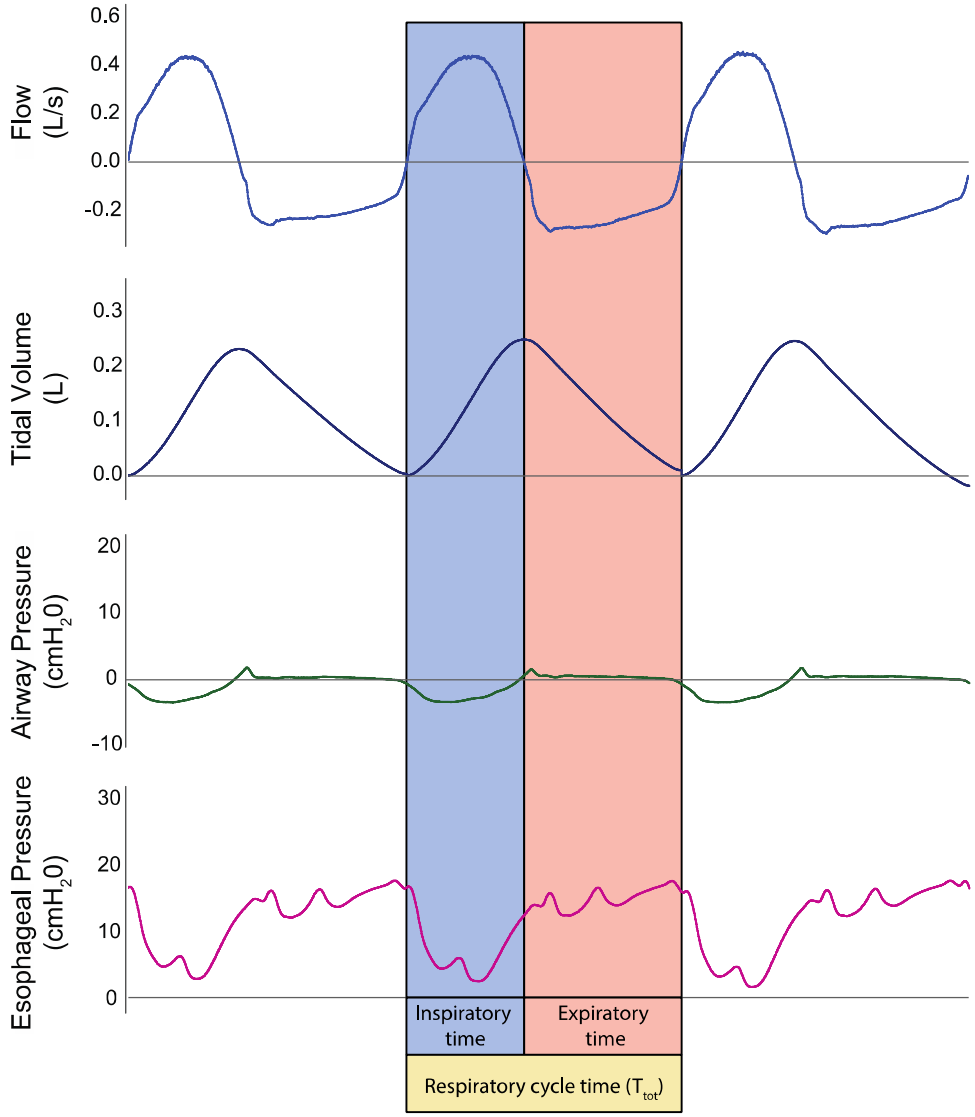
Overview of study procedures:



Note: Ketamine infusion is discontinued at 2 hours and the subsequent decrease in ketamine plasma concentration is due to the natural drug elimination from the system.

1. Supplementary Figures

Figure S1. Method of assessment of respiratory timing



This figure illustrates how respiratory timing (i.e. inspiratory-to-expiratory (I:E) ratio, inspiratory time/total respiratory cycle time (T_i/T_{tot})) was analyzed. Inspiration and expiration were defined based on flow. Data was analyzed using a spirometry algorithm that was developed based on the Spirometry add-on function (Spirometry Version: 2.5.4) in LabChart, which automatically detected zero flow periods to identify transitions between inspiratory and expiratory phases. Flow channel was filtered using a low-pass 1 Hz

filter to account for artefacts that might affect readings, respiratory times were calculated using a time-coded derived flow channel. All cyclic measurements were derived from the directly measured flow channel, inspiratory flow was calculated based the readings of tidal volume and inspiratory duration using the equation (tidal volume/inspiratory duration), and expiratory flow was calculated by (tidal volume/ expiratory duration). Minute ventilation was calculated from tidal volume and respiratory rate using the formula (tidal volume* respiratory rate). Manual cleaning was conducted for few waves that had multiple artefacts and did not align with the cycles recorded on the original flow channel.

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